

Amendments to the Specification

Please amend the specification as follows:

Please enter into the instant application the Sequence Listing being submitted concurrently herewith in response to the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures.

Please replace paragraph [010] with the following:

In other embodiments, the invention provides an isolated or purified polypeptide comprising the amino acid sequence YVGAAAV (SEQ ID NO: 16), wherein the polypeptide stimulates a protein kinase B signaling pathway. The protein kinase B can be Akt. In some embodiments, the polypeptide binds vascular endothelial growth factor receptor-2. The endothelial growth factor receptor-2 can be flk-1/KDR.

Please replace paragraph [018] with the following:

Figure 1A illustrates the exon structure of the commonly expressed VEGF₁₂₀ alternative splice variant compared to VEGF₁₆₄, VEGF₁₈₈, and the novel VEGF₂₀₅* alternative splice variant. In the Figure, boxes represent exons. VEGF₂₀₅* is encoded by exons 1-5 and contains an extended exon 6 spliced to a site that is 5' of exon 8, with the loss of exon 7. Exon 6 of VEGF₂₀₅* encodes a unique 7-amino acid carboxyl-terminal tail, YVGAAAV (SEQ ID NO: 16), that is significantly different from the carboxyl-terminal tail of other VEGF alternative splice variants that have been identified.

Please replace paragraph [025] with the following:

Figure 6 shows an amino acid sequence alignment of the VEGF alternative splice variant sequences for VEGF₂₀₅* (SEQ ID NO: 1), VEGF₁₈₈ (SEQ ID NO: 2), VEGF₁₆₄ (SEQ ID NO: 3), VEGF₁₄₄ (SEQ ID NO: 4), and VEGF₁₂₀ (SEQ ID NO: 5). The murine VEGF isoforms are aligned to show how they differ at their amino termini (shaded sequences).

Please replace paragraph [0111] with the following:

The 5'-end of VEGF_{205*} was amplified using an exon 2 forward primer (GAA GTC CCA TGA AGT GAT CAA G, SEQ ID NO: 7) and a reverse primer specific for the region downstream of exon 6 (TCC AGG GCA TTA GAC AGC A, SEQ ID NO: 8), using cDNA generated from total RNA isolated from FVB/N mouse lung tissue, yielding a product of 424 bp. To obtain the 3'-end, a primer spanning the exon 6 boundary into the immediate downstream region (TTC TGG AGC GTG TAC GTT, SEQ ID NO: 9) and a 3'-UTR reverse primer (AAA CCC TGA GGA GGC TCC TT, SEQ ID NO: 10). This was used to amplify a 250-bp product that was then gel-purified before re-amplification using a nested forward primer (TGG AGC GTG TAC GTT GGT, SEQ ID NO: 11). DNA fragments were cloned into pcDNA4/HisMax-TOPO and pCR2.1 (Invitrogen) and the DNA sequence of at least two clones was determined for each construct. The DNA fragments generated included overlap of cDNA sequence that was unique and not primer encoded.

Please replace paragraph [0113] with the following:

DNA fragments that encoded mature VEGF polypeptides were amplified by PCR using a common forward primer (GGC AGC CAT ATG GCA CCC ACG ACA GAA GGA, SEQ ID NO: 12) and specific reverse primers (VEGF₁₂₀ and VEGF₁₄₄, AGA CTC GAA TTC CTC ACC GCC TTG GCT TGT, SEQ ID NO: 13; for VEGF_{205*}, AGA CTC GAA TTC CAG GAA GGC TCC AAG GAA, SEQ ID NO: 14). Following amplification, the DNA fragments were cloned into pCR4-TOPO vector (Invitrogen) for verification by automated DNA sequencing. DNA fragments were subcloned into the *NdeI-EcoRI* restriction sites of pET-28a (Novagen, Madison, WI), which fuses an additional 21 amino acids and a His-Tag to the amino-terminus. Expression of recombinant protein was induced with 0.5 mM isopropyl β -D-1-thiogalactopyranoside in cultures of transformed *E. coli* BL21(DE3) cells (Stratagene, La Jolla, CA) grown to an optical density of 0.6 at 650 nm for 2 hr.

Please replace paragraph [0118] with the following:

The comparative exon structures of four murine VEGF alternative splice variants, including the exon structure of VEGF_{205*}, is shown in Figure 1A. In murine VEGF_{205*}, the 6 carboxyl-terminal amino acids that are present in the majority of VEGF isoforms of human, mouse, and rat, including VEGF₁₄₄, which is CDKPRR (SEQ ID NO: 15), is replaced with a unique 7-amino acid carboxyl-terminal end, YVGAAAV (SEQ ID NO: 16). (A comparison of these amino acid sequences is set forth in Figure 6.) This new variant is referred to herein as VEGF_{205*} to avoid confusion with the murine alternative splice variant, VEGF₁₄₄. The expression of a rarely expressed VEGF alternative splice variant, VEGF₂₀₆, which contains an extended exon 6 has been characterized in humans. In the present work, it was discovered that the DNA sequence of VEGF_{205*} differs from the human VEGF₂₀₆ cDNA in that in VEGF_{205*}, exon 6 is extended by 61 bases and is spliced to a unique position 120 bases upstream of exon 8. Protein translation into exon 6b occurs as an extension defined as 6', which is the 61-bp insert containing a stop codon, which results in termination of protein synthesis within this exon and mature polypeptide produced by the VEGF_{205*} consists of 145 amino acids.

Please replace paragraph [0122] with the following:

Here, we cloned and sequenced VEGF_{205*} cDNA, which we had previously identified only as an mRNA produced in murine skin papillomas and carcinomas. The exon structure of VEGF_{205*} includes exons 1-6, with exon 6 extended by 61 bases (exon 6b) and spliced to a new site 120 bases 5' of the exon 8 splice site. Protein translation of this open reading frame yielded a novel VEGF isoform of 145 amino acids. VEGF_{205*} differs from murine VEGF₁₄₄ by only the carboxyl-terminus with the 6 amino acids CDKPRR (SEQ ID NO: 15) being replaced by a unique 7-amino acid carboxyl-terminus, YVGAAAV (SEQ ID NO: 16). Thus, the positively charged and potentially kinked carboxyl-terminus found in the majority of VEGF isoforms is replaced in the novel VEGF_{205*} splice variant with hydrophobic amino acids.